Remarks:

Claims 1-8 and 20 stand rejected, under 35 USC § 112, second paragraph, as indefinite. Claims 1, 4-7, and 20 stand rejected, under 35 U.S.C. § 103, as obvious over Wen et al., in view of Juan et al. Claims 2-3 stand rejected as obvious over Wen et al., in view of Juan et al., and further in view of Watanabe et al. Claim 8 stands rejected as obvious over Wen et al., in view of Juan et al., and further in view of Maggio.

Applicants disagree with these rejections and, before addressing these rejections specifically, briefly summarize the invention for the Examiner's convenience. The currently claimed invention relates to an ELISA-based CDK activity assay which measures the amount of Rb protein phosphorylated by CDK at specific amino acid residues (see the definition of "CDK activity" on page 4, lines 13-18, of the specification). This measurement is achieved using a combination of antibodies including a first "capture antibody" which recognizes Rb phosphorylated at specific CDK phosphorylation sites (see the definition of "capture antibody" on page 4, lines 19-22, of the specification), and a second anti-Rb primary antibody which recognizes Rb regardless of phosphorylation state (see definition of "anti-Rb primary antibody" on page 4, lines 23-24, of the specification). Measurement of the anti-Rb antibody present in the capture antibody-Rb-primary antibody complex measures CDK activity by means of quantitating the CDK phosphorylated Rb. Applicants note that, while the anti-Rb antibody can recognize Rb in a phosphorylation-independent manner, only Rb phosphorylated at specific residues by CDK is present in the capture antibody-Rb-primary antibody complex. Therefore, quantitation of the anti-Rb antibody is a measure of phosphorylated Rb and CDK activity with respect to phosphorylation at the specifically named residues.] not recited in the claims.

With respect to the indefiniteness rejection, the Examiner argues that the rejected claims lack recitation of a correlation between how the resultant capture antibody anti-Rb primary antibody complex provides a measure of

CDK activity. Applicants disagree and refer the Examiner to above-described summary of the currently claimed invention. As noted above, the capture antibody recognizes only Rb phosphorylated at specific CDK phosphorylation sites. As the amount CDK activity increases, the amount of such phosphorylated Rb increases. Thus, the amount of Rb present in the capture antibody complex increases which leads to an increase in the amount of anti-Rb primary antibody present in the capture antibody-Rb-primary antibody complex, and, thus, an increase in the signal detected in the assay. Accordingly, Applicants request withdrawal of this rejection.

claimed correlation not recited

Turning to the obviousness rejection of claims 1, 4-7, and 20 over Wen et al. (hereinafter "Wen") in view of Juan et al. (hereinafter "Juan"), Applicants disagree and point out that Wen is merely an assay for detecting total Rb. Wen does not disclose or suggest the specific Rb residues targeted for assessment of CDK activity by the present invention. Furthermore, Wen neither discloses nor suggests the existence of the CDK "capture antibodies" used in the present invention, which specifically recognize Rb phosphorylated at these specific CDK-mediated residues, or that such antibodies could be successfully used to capture CDK-phosphorylated Rb as a means of assessing CDK activity in combination with an anti-Rb antibody. Rather, Wen merely uses two different antibodies that recognize Rb in a phosphorylation-independent manner to measure total Rb. While Wen refers to one of the antibodies as a capture antibody, the antibody used to perform the capture function in Wen recognizes only total Rb and is distinct from the capture antibody of the present invention.

Even assuming that there is motivation to combine Wen and Juan, the deficiencies of Wen are not cured by Juan. Juan discloses an assay for monitoring Rb phosphorylation by incubating cells with dual fluorochrome-tagged antibodies. While one antibody assesses total Rb, a second antibody is specific for underphosphorylated Rb and recognizes an epitope between amino

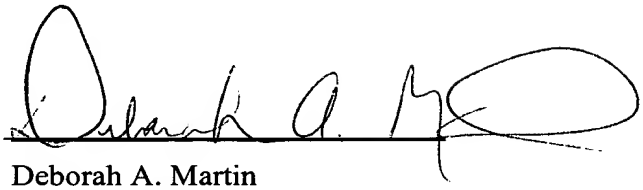
acids 514 and 610 (see page 107, right column). Rb phosphorylation is assessed by comparing the dual fluorochrome signals that represent either total Rb or underphosphorylated Rb. With respect to the phosphorylation-dependent antibody, Juan merely discloses an antibody completely distinct from the "capture antibody" of the present invention. The Juan phosphorylation-related antibody recognizes an underphosphorylated Rb, rather than the specifically CDK-phosphorylated Rbs recognized by the capture antibody of the present invention. Indeed, the Juan antibody recognizes Rb at a portion of the Rb distinct from where the capture antibodies of the present invention recognize a phosphorylated Rb. Furthermore, Juan uses its antibodies to measure dual readouts rather than a single readout in an ELISA-based dual antibody-complex assay. Juan in no way discloses or suggests that Rb is phosphorylated by CDKs at the residues recognized by the capture antibodies of the present invention, that antibodies specific for detecting CDK at these residues exist or can be made, or that such antibodies could be successfully used as a capture antibody, in combination with an anti-Rb primary antibody, to detect CDK phosphorylation at these specific sites using an ELISA based format. Thus, applicants respectfully request that this rejection be withdrawn.

With respect to the rejection of claims 2 and 3 as obvious over Wen, in view of Juan, and further in view of Watanabe et al. (hereinafter described as "Watanabe"), Applicants note that the same deficiencies described above with respect to Wen and Juan apply to the rejection of claims 2 and 3. Turning to the Watanabe reference, Applicants submit herewith a Declaration, under 37 C.F.R. § 1.131, by co-inventors Barbara A. Foster and Farzan Rastinejad, stating that Applicants' invention was conceived and reduced to practice prior to July, 1999, and, thus, prior to the publication of Watanabe. Accordingly, applicants respectfully request the withdrawal of this rejection.

Claim 8 is rejected as obvious over of Wen, in view of Juan, and further in view of Maggio. Applicant notes that Maggio merely discloses a general discussion of ELISA-based assays using a solid phase/test plate. Maggio does not disclose or suggest the particular antibodies used in the present invention, or their use in the ELISA-based assay of the present invention. Applicants request withdrawal of this rejection as well.

Respectfully submitted,

Date: May 5, 2003



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PENDING CLAIMS

1. A method for measuring cyclin-dependent kinase (CDK) activity in a sample, said method comprising:
i) contacting said sample with an anti-retinoblastoma protein (Rb) capture antibody and isolating the capture antibody-Rb complex;
ii) contacting said capture antibody-Rb complex with an anti-Rb primary antibody and isolating the capture antibody-Rb-primary antibody complex; and
iii) measuring the amount of CDK-phosphorylated Rb in said sample by quantitating the primary antibody present in said capture antibody-Rb-primary antibody complex.

2. The method of claim 1, wherein said CDK is CDK2.

3. The method of claim 1, wherein said CDK is CDK4.

4. The method of claim 1, wherein said method measures intracellular CDK activity.

5. The method of claim 4, wherein said method measures CDK activity in a cultured cell.

6. The method of claim 4, wherein said method measures *ex vivo* CDK activity in a cell taken from an animal.

7. The method of claim 1, wherein said CDK activity is human CDK activity.

8. The method of claim 1, wherein said capture antibody is bound to a test plate.

20. The method of claim 4, wherein said method measures *ex vivo* CDK activity in a cell taken from an animal.